A rusty and sweet side of sepsis

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Iron based sculpture by Portuguese Artist Rui Chafes 'Extinguish my eyes' (2005). Credit: Rui Chafes

Sepsis is a major global healthcare problem that affects over 18 million individuals per year, every single year, corresponding to 1,400 deaths per day. In Europe and the US alone, there are an estimated 135,000 and 215,000 causalities and €7.6 and €17.4 billion related treating costs, respectively.

Using experimental models of sepsis in mice the research team led by Miguel Soares at the Instituto Gulbenkian de Ciência in Portugal discovered an unsuspected mechanism that is protective against sepsis. This study that provides new avenues for therapeutic approaches against sepsis appears in the June 15 issue of the prestigious scientific journal *Cell*.

Despite being more common than heart attack and more lethal than cancer, the large majority people do not really know what sepsis is. Briefly, it consists of an uncontrolled body's response to an infection that is spreading towards different parts of the body, also know as a systemic infection. The immune system of the infected individual does try to kill the microbes responsible for the infection, and in many cases manages to do so, but in the process causes profound alterations in the normal functioning of vital organs, such as, the brain, heart, liver, kidney or lungs. In more severe cases blood pressure also drops and those organs ultimately stop functioning properly and as a result the patient dies.

It is well know that sepsis patients vary in their response to infection and disease severity, depending on the type of infection as well as on their

genetic characteristics, coexisting illnesses and age. A long lasting unsolved mystery relates to why despite an effective control of the infectious microorganisms by the use antibiotics, some patients succumb while others recover from the infection. Over the past five years the research team led by Miguel Soares has put forward the concept that those individuals that do not succumb to sepsis develop a protective response that maintains the function of vital organs, conferring disease tolerance to the infection. Using experimental models of sepsis in mice they now discovered a mechanism that is vital to confer disease tolerance to sepsis.

"We knew that a key element to promote disease tolerance to infection is how the levels of iron are controlled in different tissues while other colleagues had shown that the pathogenesis of sepsis is associated with deregulation of glucose (sugar) metabolism. What we found is that these two phenomena are intimately linked in that controlling iron metabolism is required to sustain the production of glucose in the liver so that glucose can be used as a vital source of energy by other organs", says Miguel Soares.

Sebastian Weis a Medical Doctor doing is post-doctoral training with Miguel Soares induced sepsis in laboratory mice and compared how disease progresses in mice that express or not ferritin, a protein that controls iron in the liver. He found that ferritin is absolutely required for the liver to produce glucose after an infection and hence to protect mice from succumbing to sepsis.

"Typically in mice, after infection, there is an increase of blood glucose levels followed by a quick drop, which can become lethal. In humans with infectious disease this also occurs in a subset of patients and is know to lead to higher death rates. Our results showed that ferritin controls glucose production in the liver so that blood glucose levels are maintained within a range that allows survival. Without ferritin, the

glucose levels continued to drop and mice eventually die from sepsis", explains Sebastian Weis, co-first author of the manuscript and currently a researcher and clinician at the Jena University Hospital, Germany, where part of the experiments were conducted."

Another key piece of this puzzle was provided by Ana Rita Carlos, a PhD working as a post-doctoral fellow with Miguel Soares. She found that the reason why ferritin is required for the liver to produce glucose relies on a molecular mechanism that controls the expression of one of the key genes involved in this process, known as glucose 6 phosphatase. When ferritin is absent, iron deregulates the expression of Glucose 6 phosphatase and the liver loses its capacity to secrete glucose. When this occurs, glucose cannot be delivered and used by other vital organs as a source of energy. This is required to maintain the function of those organs in response to infection and as such to prevent the development of lethal forms of sepsis. This protective mechanism does no influence the microorganisms that are the underlying cause of the disease and as such is said to confer disease tolerance to sepsis.

"It is very interesting that while essential to support many vital cellular functions iron must be tightly controlled in the liver so that it cannot interfere with the production of glucose. The molecular mechanism via which this occurs relies on the expression of ferritin, a protein complex that binds iron and devoid iron from interfering with glucose production " explains Ana Rita Carlos, also a co-first author of the manuscript.

"This is a great example on how basic research conducted in a multidisciplinary environment such as the one provided by the Instituto Gulbenkian de Ciência, without an immediate commercial interest, can have a global impact on the treatment of a major disease that affects over 18 million individuals per year worldwide. Our mission is to make discoveries so that these can be eventually translated into treatments of major diseases". says Miguel Soares.

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